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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/788,286 | 02/16/2001 | Michael B. Goshe | 23-56765 | 5274 |

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EXAMINER

CEPERLEY, MARY

ART UNIT

PAPER NUMBER

1641

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/788,286

Applicant(s)

GOSHE ET AL.

Examiner

Mary (Molly) E. Ceperley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 15-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-14 and 24-27 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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(1) The invention disclosed in the instant application is directed to a method of assessing the phosphorylation states of proteins using the conventional method of the prior art which involves the sequential steps of **(a)** dephosphorylating the targeted proteins by a well known beta-elimination reaction, **(b)** the Michael addition reaction of the dephosphorylated products with differentially isotopically labeled dithiol reactants, followed by **(c)** labeling with a conventional detectable label or solid phase. The novelty of the invention is alleged to reside in the use of a "presynthesized" reagent wherein this reagent is inclusive of the chemical moieties required to effect steps **(b)** and **(c)** (specification, page 14, lines 10-12).

(2) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

(3) Claims 1-14 and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over **(a)** Weckwerth et al (Rapid Commun. Mass Spectrom. **14**, 1677-1682 (2000)) taken in combination with each of **(b)** Gygi et al (Nature Biotechnology, **17**, 994-999 (1999)) or Aebersold et al (WO 00/11208).

Weckwerth et al in Figure 1 describe a method of comparing the phosphorylation states of proteins which comprises the steps of beta-elimination of the phosphate groups of serine and/or threonine ("formerly phosphorylated") followed by the Michael addition of ethanethiol and isotopically labeled ethanethiol (ICATs) to differentially label the dephosphorylated proteins ("differentially labeled with stable isotopes"). This is the same method which is outlined in FIG. 2, A) through C) of the instant application. However, the method of the instant invention uses a "presynthesized" reagent "B-L-PhRG" to effect the same method steps as the process of the reference. In the instant invention, the phosphate reactive group "PhRG" corresponds to the thiol of the ethanethiol reactant of the Weckwerth method, the

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group "L" corresponds to the differentially isotopically labeled ethane moiety of the ethanethiol reactant, and the binding agent "B" corresponds to a moiety used to attach the reagent to a column (see page 5, lines 6-9 of the instant specification). The LC/MS detection of the reference corresponds to the steps of "capturing" (by binding to the LC column), "releasing", "detecting" and "comparing" recited in instant claim 1. Thus, the Weckwerth et al method involves the same sequence of reactions as the instantly claimed method but does not use a "presynthesized" reagent.

Gygi et al describe the use of "presynthesized" biotin-labeled ICATs containing an additional reactive functionality, which correspond to the reagent "B-L-PhRG" of the instant invention, to differentially label proteins. See page 994, the first full paragraph of the second column; Figures 1 and 2. Note that the Gygi et al method is described as being generally applicable to the determination of "protein expression in different cell states"; see page 997, first column second full paragraph; page 998, the last paragraph of the first column. Aebersold et al similarly describe the use of a "presynthesized" labeled ICAT reagent containing an additional reactive functionality to label proteins. See the reagent "A-L-PRG" of page 5; the affinity tags of page 11-12; determination of the extent of phosphorylation of proteins; page 25; Scheme 2 of page 75. Aebersold et al specifically describe the "reacting", "capturing", "releasing", "detecting", and "comparing" steps of instant claim 1 (see claims 1, 13 and 15).

In view of the fact that "presynthesized" labeled ICAT reagents are well known in the art for use in differentially labeling proteins and to establish "protein expression in different cell states" including the extent of phosphorylation of proteins (Gygi et al and Aebersold et al), it would be obvious to modify the multi-step method of Weckwerth et al by employing a "presynthesized" reagent as described by Gygi et al or Aebersold et al, as claimed, with the expectation of obtaining a simplified and similarly useful method for comparatively determining the extent of phosphorylation of proteins in a sample. This is particularly true in light of the Aebersol et al disclosure of the same sequence of "capturing", "releasing", "detecting", and "comparing" steps as are used in the method of instant claim 1.

The features of the dependent claims are either specifically described by the references (e.g. for the use of mass spectrometry as a detection method {claim 2}, see Weckwerth et al; for the

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determination of the phosphorylation states of serine or threonine {claim 5}, see Weckwerth et al; for the use of cell-derived samples {claim 10}, see Aebersold et al: page 32, the second full paragraph) or constitute obvious variations in parameters which are routinely modified in the art (e.g. choice of sample types {claim 12}) and which have not been described as critical to the practice of the invention.

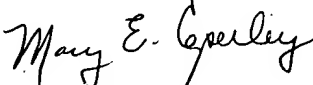
(4) Adamczyk et al (Rapid Communication in Mass Spectrometry, **15**(16), 1481-1488 (2001)) is cited to further show the state of the art.

(5) Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. (Molly) Ceperley whose telephone number is (703) 308-4239. The examiner can normally be reached from 8 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached at (703) 305-3399. The fax phone number for responses to be filed BEFORE final rejection is (703) 872-9306. The fax phone number for responses to be filed AFTER final rejection is (703) 872-9307.

Questions which are NOT RELATED TO THE EXAMINATION ON THE MERITS, should be directed to **TC 1600 CUSTOMER SERVICE** at **(703) 308-0198**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

June 29, 2003


Mary E. (Molly) Ceperley
Primary Examiner
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